TOXICOLOGY FORUM

1990 Annual Winter Meeting

February 19-21, 1990
L'Enfant Plaza Hotel
Washington, D.C.

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DR. KABAT: Thank you.

The problem of passive smoking and lung cancer has provoked a good deal of debate both on a scientific and on a public policy level. Do the studies that purport to show an association of exposure to environmental tobacco smoke (ETS) and lung cancer occurring in lifetime nonsmokers provide adequate evidence to resolve the issue? As Nancy Haley has just shown, she and her colleagues are very good at measuring recent exposure to ETS using cotinine measured in saliva, serum, and urine. Unfortunately, these biomarkers are not helpful for assessing exposure over the several decades relevant to the induction of lung cancer. Given the lack of a biomarker for long-term exposure to ETS, epidemiologic studies have had to rely on self-reports or proxy-reports of ETS exposure.

I propose to raise what I consider to be some of the key aspects of the roughly 15 epidemiologic studies of the issue of ETS and lung cancer and to point out certain areas that require further study. I will briefly refer to our own study which is still in progress at the American Health Foundation. Finally, I will suggest a possible direction for further study of this issue.

EPIDEMIOLOGIC

Table 1 lists studies examining the lung cancer risk of non-smoking wives of smoking husbands compared to the non-smoking wives of non-smoking husbands. One notes that the greatest magnitude of the overall relative risk (RR) is 2.1. After the Trichopoulos and Correa studies, the highest RR is 1.65 (Lam et al.). The national Research Council's committee on passive smoking carried our a meta-analysis of the existing studies in 1986 and came up with an overall RR of 1.34 (95% confidence interval: 1.18-1.53) (1).

In four out of the fifteen studies listed, the overall RR is statistically significant. When one examines the data by level of exposure, i.e., number of cigarettes per day smoked by the husband stratified into two or more levels, 8 of the 15 studies show evidence of a dose-response relationship.

HISTOLOGY

When we look at the effect of ETS exposure by histologic type, we see an interesting discrepancy (Table 2). Dalager et al. (2) and Pershagen et al. (3) show roughly comparably elevated odds ratios (OR) for squamous cell and small cell carcinomas combines, but not for adenocarcinoma. In contrast, Lam et al. (4) obtained a significant effect for adenocarinoma but not for squamous cell carcinoma.

The results of Hirayama's study (5) presumably agree on this point with those of Lam et al., since the majority of his lung cancer cases were apparently adenocarcinoma. Trichopoulos et al. results (6) presumably weigh in on the side of Dalager et al. and Pershagen et al., since Trichopoulos excluded adenocarinoma and terminal bronchial carcinoma from their series.

Since adenocarinoma occurs more commonly in never smokers than in smokers and generally more commonly in women than in men (7), one would expect that if ETS exposure is an appreciable risk factor for lung cancer, it is associated with adenocarcinoma, as well as possibly with other types. The inconsistency in the results to date regarding histology indicates that this is one area that merits further study.

ASSESSMENT OF DISEASE STATUS

Misclassification on disease status occurs when diagnoses other than primary carcinoma of the lung are included in the case series or when a primary cancer of the lung is included among the controls due to its having gone undetected. Garfinkel et al. reported that of 283 women listed as having lung cancer in hospital records but with no mention of their having smoked, 36 (12.7%) turned out to have diagnoses other than lung cancer when the histology was reviewed by one of the authors (8).

In studies in which histologic verification of lung cancer is a criterion for inclusion in the study, misclassification should be minimal. However, some of the studies listed in Table 1 were lacking this for all cases.

It should also be mentioned that even when lung cancer is histologically verified, it is possible that some cases judged to be primary cancer of the lung are actually secondary to a cancer of another site that has gone undetected.

ASSESSMENT OF EXPOSURE STATUS

This is a greater problem than assessment of disease status, and for some investigators it is the key problem of epidemiologic studies of ETS and lung cancer (9,10).

Misclassification of exposure status can occur in a number of ways. First, subjects who have smoked for some period of their life can be erroneously included in a study of never smokers. Second, subjects may under-report (minimize) or over-report (inflate) their ETS exposure, or this may be done by proxies. A third type of misclassification can occur when some indirect measure (such as whether the subject is married to a smoker or how much the spouse smokes) is used as an indicator of ETS exposure. The effect of misclassification on the estimate of the RR depends on whether the misclassification is random or differential (that is systematic). Random misclassification will bias the estimate of the RR toward the null, thus making an effect, if there is one, more difficult to detect. If misclassification on exposure differs between cases and controls, the estimate of the RR can be biased either upwards or downwards depending on the direction of the bias (11).

Misclassification of active smokers as never smokers.

Garfinkel and co-workers found that among lung cancer cases identified as "nonsmokers" or lacking any mention of smoking in the hospital record, 40% were revealed to have smoked upon reinterview (8). Although a detailed personal interview yields more accurate smoking histories than reliance on hospital charts, it is still likely that, even when subjects are directly interviewed and more so when various proxies are used, some misclassification of smokers as nonsmokers occurs.

Lee has argued that random misclassification of smokers as non-smokers coupled with a tendency of smokers to marry smokers could account for the observed association of a spouse's smoking and increased lung cancer risk in non-smoking spouses (9). Assuming a 5% misclassification of smoking subjects, a RR of 20 for active smoking, no true effect of passive smoking, and a between-spouse smoking concordance of 3.45, Lee demonstrates the effects of such a bias. These include an apparent effect of passive smoking (RR = 1.75) and the creation of a large proportion of true smokers among the self-reported non-smokers with lung cancer.

Misclassification of self-reported ETS exposure.

A study by Pron et al. (12) suggests that misclassification of self-reported ETS exposure may be extensive. They examined the reliability of responses in 117 control subjects who had participated in a study of passive smoking and who were reinterviewed on average six months later. Responses to an initial question about exposure to ETS (yes/no) were more reliable for exposure at home than at work (Table 3). Reproducibility of questions concerning exposure to a spouse's smoke (yes/no) was high for both sexes, with the reliability being generally lower for other family members. Quantitative measures of ETS exposure, i.e., number and duration of exposures, were generally less reliable than qualitative (or dichotomous) measures. In general, non-smokers gave more reliable information on all parameters of ETS exposure than smokers.

Unfortunately the study by Pron et al, did not examine the reliability of responses among cases as well as among controls. In case-control studies particularly one must be concerned that the case's reporting of exposure may be influenced by his diagnosis. In a study of lung cancer occurring in non-smokers, this could take the form of cases probing past exposures more intensively than controls and over-reporting exposures to ETS, since some cases may feel compelled to find an explanation for their disease. On the other hand, it is also possible that cases might minimize their exposures out of an unwillingness to blame a spouse.

Misclassification due to use the spouse's smoking habits.

Using the presence of a smoking spouse as an indicator of ETS exposure can lead to serious misclassification of exposure. Based on a survey of nearly 38,000 never- and ex-smokers, Friedman et al. (13) reported that the sensitivity and specificity of using the presence of a smoking spouse as a predictor of actual ETS exposure were quite poor. Thirty-nine percent of men and 47% of women married to smokers reported zero hours of exposure at home. Conversely, 49% of men and 41% of women married to non-smokers reported some ETS exposure.

CONFOUNDING

Confounding is another major problem area for the evaluation of epidemiologic studies of ETS and lung cancer and one that has received relatively little attention.

Several studies suggest that a variety of factors could act as confounders of an ETS-lung cancer association. Friedman (13) found that age bore a strong negative relationship to reported ETS exposure. Hours per week of ETS exposure were associated with alcohol consumption, marijuana use, being currently unmarried, and, in a U-shaped fashion, with "no college education."

Koo, Ho, and Rylander (14) examined a wide variety of behaviors of the non-smoking wives of smoking and non-smoking husbands in Hong Kong. They concluded that in general wives with husbands who had never smoked had healthier lifestyles than wives with smoking husbands. Specifically, the former were of higher socioeconomic status, were more conscientious housewives, ate better diets, and had higher indices of family cohesiveness as well as better health status.

A third study, by Sidney et al. (15) reported that dietary B-carotene intake was significantly lower in non-smokers exposed to passive smoke at home than in non-smokers who were not exposed, after adjustment for ag e, sex, race, education status, body weight, and alcohol intake.

They concluded that dietary B-carotene intake was a potential confounder of the relationship between ETS and lung cancer.

Other potential confounders included: occupation, domestic radon exposure, a history of exposure to therapeutic x-rays, and keeping pet birds in the home. This last is raised by a recent study from the Netherlands which found that the odds ratio for lung cancer among people who kept pet birds in their home was 6.7 (95% confidence interval 2.2-20.0) after adjustment for active smoking and vitamin C intake (16). This study did not assess ETS exposure among the subjects.

THE AMERICAN HEALTH FOUNDATION STUDY

Since 1983, a study of ETS and lung cancer in never smokers has been in progress at the American Health Foundation. All lung cancer cases interviewed in the context of a large, multi-center study of tobacco-related diseases who report never having smoked more than one cigarette per day for a year are given a detailed ETS questionnaire.

For each case, 2-3 hospitalized controls who have diagnoses not known to be associated with tobacco use and who are also lifetime non-smokers are interviewed. Controls are matched to cases on age (+/- 5 years), sex, race, hospital, and date of interview (within 3 months).

The items in the questionnaire include exposure in utero; in childhood (specific family members who smoked, years of exposure and average number of hours of exposure per day, and a subjective rating of the intensity of exposure), in adulthood at home (specific family members who smoke(d), number of cpd smoked by each, years of exposure, number of hours per day, subjective rating of exposure, and where a spouse smoked, whether he or she smoked in the bedroom); in the workplace (number of hours per week, years of exposure, number of smokers within ten feet of subject, rating of exposure) for up to four different jobs; and in various forms of transportation and in social situations.

In addition to ETS questions, information is obtained on demographic factors, occupation, alcohol consumption, medical history, diet, and other factors. To date, this study has accrued a total of 90 lung cancer cases and 247 matched controls. We plan to continue recruiting subjects for the study in order to reach a sample size of 150 cases. Table 4 gives a breakdown of the histology of lung cancer by sex.

Preliminary analyses of the data do not indicate any striking ETS exposure differences between cases and controls. Tables 5 and 6 give crude odds ratios and confidence intervals for overall exposure in childhood, adulthood at home, and in the workplace, in males and females, respectively. With the possible exception of exposure in childhood and among women, there is little suggestion of excess risk due to ETS. A fuller analysis of these data, including adjustment for covariates, is in progress.

CONCLUSION

Epidemiologic studies of ETS and lung cancer generally suffer from small sample size. Given the small magnitude of the observed RR associated with passive smoking and the problems associated with multiple histologic types bias, misclassification, and confounding, increasing the sample size is one way to attempt to answer the ETS-lung cancer question with greater certainty. A case-control study of 10,000 lung cancer cases (7,500 males and 2,500 females) could be expected to

yield approximately 150 male and 250 female never smokers, based on estimates of the frequency of lung cancer among never smokers (2% for males and 10% for females [7]). Table 7 shows the sample sizes necessary in each group (assuming equal numbers of cases and controls) to detect RRs between 1.25 and 2.00, with a one-tailed alpha of 5% and 80% power, given various proportions of exposed controls.

While it is highly unlikely that such a study would be funded solely to assess the effects of ETS exposure, the study could be designed to make an important contribution to the radon-lung cancer issue as well. Specifically, studies of domestic radon exposure have also suffered from small sample sizes and have produced variable and unstable estimates of the risk of radon exposure in never smokers. In addition, there is a need to better assess the interactive effects of active smoking and radon exposure. Since ETS and radon exposure are both risk factors for lung cancer, and since one may confound, or interact with, the other, a large study designed to measure both factors as reliably as possible would have considerable scientific merit.

Table 1

Epidemiologic Studies

Prospective Studies	*Relative Risk*	*95% C.I.*
Hirayama (1981)	1.63	1.25 - 2.11
Garfinkel (1981)	1.18	0.90 - 1.54
Case-Control Studies		
Trichopoulos, et al. (1981)	2.1	1.18 - 3.78
Chan & Fung (1982)	0.75	0.44 - 1.30
Correa, et al. (1983)	2.03	0.83 - 5.03
Koo, et al. (1983)	1.54	0.90 - 2.64
Kabat & Wynder (1984)	0.79	0.26 - 2.43
Wu, et al. (1985)	1.2	0.6 - 2.5
Garfinkel, et al. (1985)	1.12	0.74 - 1.69
Lee, et al. (1985)	1.03	0.41 - 2.47
Akiba, et al. (1986)	1.48	0.88 - 2.50
Dalager, et al. (1986)	1.5	0.8 - 2.8
Pershagen, et al. (1987)	1.28	0.75 - 2.16
Lam, et al. (1987)	1.65	1.16 - 2.35
Koo, et al. (1987)	1.55	0.94 - 3.08

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Cell Type Related to Spouse's Smoking

Study	*Histologic Type*	*N*	*Odds Ratio*	*95% C. I.*
Dalager et al. (1986)	Adenocarcinoma	16	1.02*	0.33 - 3.16
	Squamous & Small Cell Ca.	14	2.88*	0.91 - 9.10
	Other	18	1.31*	0.48 - 3.57
Pershagen et al. (1987)	Squamous or Small Cell Ca.	20	3.3	1.1 -11.4
	Other	47	0.8	0.4 - 1.5
Lam et al. (1987)	Adenocarcinoma	131	2.12	1.32 - 3.39
	Squamous Cell Ca.	27	0.85	0.35 - 2.06
	Small Cell Ca.	8	3.00	0.53 -16.9

* Adjusted for gender, age, and study area.

Table 3

Reproducibility of ETS Exposure Data

Question	*Kappa value*
Ever lived with regular smoker?	0.66
Ever exposed to smoke at work?	0.46
No. of resident smokers?	0.55
No. of job sites reported?	0.37
Duration of residential exposure?	0.45

Source: Pron et al., 1988

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Histology of Lung Cancer Among Never-Smokers

	Males		*Females*	
	N	(%)	N	(%)
Squamous & Small Cell Ca.	5	(13.5)	10	(18.9)
Adenoca.	25	(67.6)	26	(49.1)
Large Cell Ca.	5	(13.5)	6	(11.3)
BAC	1	(2.7)	7	(13.2)
Other	1	(2.7)	4	(7.5)
	37		53	

Table 5

American Health Foundation Study

Males

		Cases	Controls	OR	95% C.I.
Exposed in Childhood:					
	No	15	36	1.00	-----
	Yes	21	69	0.73	0.34 - 1.59
Exposed in Adulthood-at home:					
	No	23	68	1.00	-----
	Yes	13	32	1.20	0.54 - 2.68
Exposed at Work (ever):					
	No	16	45	1.00	-----
	Yes	21	60	0.98	0.46 - 2.10

Table 6

American Health Foundation Study

Females

		Cases	Controls	OR	95% C.I.
Exposed in Childhood:					
	No	17	61	1.00	-----
	Yes	36	77	1.68	0.86 - 3.27
Exposed in Adulthood-at home:					
	No	18	45	1.00	-----
	Yes	35	97	0.90	0.46 - 1.76
Exposed at Work (ever):					
	No	17	43	1.00	-----
	Yes	27	68	1.00	0.49 - 2.06

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Table 7

Power Calculation

Odds Ratio To Detect	Percent Controls Exposed		
	20%	40%	60%
1.25	1616	1124	1172
1.50	419	303	329
1.75	214	161	179
2.00	134	104	119

$\alpha = .05$ (1-tailed) 1-B=.80 R = 1

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